REMARKS

In the Office Action dated January 24, 2007, claims 1-43 are pending, of which claims 26-43 are withdrawn from further consideration as allegedly drawn to non-elected subject matter. Claims 11-13 and 25 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Claims 1-14, 17, 19-22 and 24 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by Esenaliev (U.S. Patent No. 6,165,440). Claims 15 and 16 are rejected under 35 U.S.C. §103(a) as allegedly obvious over Esenaliev in view of Finkelstein (U.S. Patent No. 4,657,763). Claim 18 is rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Esenaliev in view of Lang, Jr. et al. (U.S. Patent No. 4,515,954). Claim 23 is rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Esenaliev in view of Patel (U.S. Pub. No. 2005/0180917). Claim 25 is rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Esenaliev in view of Cash, Jr. et al. (U.S. Patent No. 6,125,295). Further, the Examiner has objected to Applicants' claim for priority. Additionally, the Examiner has alleged that the Information Disclosure Statement filed on December 19, 2003 fails to comply with 37 C.F.R. §1.98(a)(2).

This Response addresses each of the Examiner's rejections and objections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

With respect to Applicants' claim for priority, the Examiner alleges that Applicants have not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. §120. The Examiner states that to receive the benefit of priority under 35 U.S.C. §120, 121 or 365(c), Applicants must include a reference to the earlier application(s) and the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications. The Examiner states that if the reference (including the relationships) was

included in a previous submission (e.g., in the oath or the application transmittal data), it is still necessary for Applicants to amend the specification to include such reference.

Applicants respectfully submit that the cross-reference section in the present specification, as originally filed, already included references to prior applications, Serial No. 10/387,059 and Serial No. 09/363,204. By way of the instant amendment, Applicants have amended this cross-reference section to clarify that the present application is a continuation-in-part application of Serial No. 10/387,059, and is also a continuation-in-part application of Serial No. 09/363,204. A reference to these prior applications (including the relationships) was included in the application transmittal data, filed on November 10, 2003, and was also recognized in the filing receipt from the Patent Office. Applicants note, however, that the filing receipt inaccurately states that Serial No. 10/387,059 is a continuation in part of Serial No. 09/363,204. Although the present application is a continuation-in-part application of both Serial No. 10/387,059 and Serial No. 09/363,204, there is no relationship between Serial No. 10/387,059 and Serial No. 09/363,204. Applicants have filed a request with the Patent Office to correct the filing receipt in this regard. In view of the foregoing, Applicants respectfully submit that the requirements to receive the benefit of priority under 35 U.S.C. §120, 121 or 365(c) have been met.

With respect to the Information Disclosure Statement (IDS) filed December 19, 2003, the Examiner states that the provisions of §37 C.F.R. 1.98(a)(2) require a legible copy of each non-patent literature publication or that portion which caused it to be listed. The Examiner states that the literature references listed in the IDS have not been considered, apparently because Applicants did not submit copies of these literature references.

Applicants respectfully submit that 37 C.F.R. §1.98(d) states:

> A copy of any patent, publication, pending U.S. application or other information, as specified in paragraph (a) of this section, listed in an information disclosure statement is required to be provided, even if the patent, publication, pending U.S. application or other information was previously submitted to, or cited by, the Office in an earlier application, unless:
>
> (1) The earlier application is properly identified in the information disclosure statement and is relied on for an earlier effective filing date under 35 U.S.C. 120; and
> (2) The information disclosure statement submitted in the earlier application complies with paragraphs (a) through (c) of this section.

In the IDS filed December 19, 2003, Applicants clearly stated that all the references cited therein were previously submitted to the Examiner in connection with the parent case, U.S. Serial Number 10/387,059, filed on March 12, 2003. Therefore, it is respectfully submitted that Applicants have fulfilled the requirements 37 C.F.R. §1.98(d) and therefore are not required to submit copies of the references. Consideration of all the references listed in the IDS filed December 19, 2003, and return of the PTO-1449 Form with the Examiner's initialed name, are respectfully requested.

Turning to the claims, Applicants wish to draw the Examiner's attention to the amendments to the claims. Specifically, claims 26-43 are canceled without prejudice. Applicants reserve the rights to pursue the subject matter of these canceled claims in a divisional application. Independent claims 1 and 2 have been amended to further delineate the forms of radiation. Support for such amendment is found in original claim 24, for example. Claim 24 is therefore canceled in view of the amendment to claims 1-2. New claims 44-68 are added and are supported by original claims 1-25. Independent claim 44, however, defines the method as "consisting of" administering an amount of metal nanoparticles to the animal and subsequently

irradiating the animal with radiation directed to the tissue or the population of cells. It is respectfully submitted that no new matter is introduced by the foregoing amendments.

Claims 11-13 and 25 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Claims 11-13 recite the limitation "the metal cores", which allegedly lacks sufficient antecedent basis. Furthermore, the Examiner contends that it is unclear as to what Applicants intend to claim in claim 25, since the limitation recites radiation "in the form of" x-rays.

Applicants have amended claims 11-13 to delete the article "the" before the term "metal cores", and to replace the term "size" with the plural form "sizes". As to claim 25, it is believed that the claim is clear and Applicants do not understand the basis for the Examiner's rejection. In any event, claim 25 has been amended to add the recitation "at a dose" after the term "x-ray".

Applicants respectfully submit that the claims, as presently amended, are not indefinite. Accordingly, the rejection under 35 U.S.C. §112, second paragraph, is overcome. Withdrawal of the rejection is respectfully requested.

Claims 1-14, 17, 19-22 and 24 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by Esenaliev (U.S. Patent No. 6,165,440).

According to the Examiner, Esenaliev discloses the use of nanoparticles with various forms of radiation for enhancing drug delivery to tumors. The Examiner also alleges that Esenaliev teaches nanoparticles with metal cores of 0.1 nm to about 7000 nm, and that the radiation applied may be in the form of microwave, optical or RF.

Applicants respectfully submit that independent claims 1 and 2 have been amended to further define the form of radiation as selected from the group consisting of x-rays, microbeam

arrays of x-rays, radioisotopes, electrons, protons, ion beams, and neutrons. It is respectfully submitted that Esenaliev does not teach anywhere using any of the recited form of radiation in connection with nanoparticles for therapeutic purposes. A rejection of a claim under 35 U.S.C. §102(b) requires that the single prior art reference disclose every element of the claim. The absence from the reference of any claimed element negates anticipation. Kloster Speedsteel AB v Crucible Inc., 793 F.2d 1565, 1571, 230 USPQ 81, 84 (Fed. Cir. 1986). Here, Esenaliev does not teach each and every element of the method as claimed in claim 1 or claim 2 or their dependent claims.

In view of the foregoing, it is respectfully submitted that the rejection of claims 1-14, 17, 19-22 and 24 under 35 U.S.C. §102(e) based on Esenaliev is overcome. Withdrawal of the rejection is respectfully requested.

Claims 15 and 16 are rejected under 35 U.S.C. §103(a) as allegedly obvious over Esenaliev (U.S. Patent No. 6,165,440) in view of Finkelstein (U.S. Patent No. 4,657,763).

The Examiner admits that Esenaliev fails to disclose the use of thioglucose to form the surface layer on a nanoparticle. However, the Examiner contends that Finkelstein teaches the combination of gold with thioglucose such that a sufficient dosage of the gold compound is administered to effect an inhibitory action on diseased tissue, and invoke substantial remission of a disease.

Applicants respectfully submit that in light of the instant amendment, Esenaliev fails to provide sufficient teaching as a primary reference to support an obviousness rejection of claims 15-16. As submitted above, independent claims 1 and 2 have been amended to further define the form of radiation as selected from the group consisting of x-rays, microbeam arrays of x-rays, radioisotopes, electrons, protons, ion beams, and neutrons. Esenaliev does not teach

anywhere using any of the recited form of radiation in connection with nanoparticles in a radiation therapy.

Additionally, the teaching of Esenaliev would not have provided those skilled in the art with any motivation, or any reason, to use any of the forms of radiation presently recited in the claims. Specifically, Applicants observe that Esenaliev teaches irradiating particles by pulsed laser light (in the range of 0.2 μm to 2 μm) or microwaves to heat the particles, or by ultrasound to agitate the particles. According to Esenaliev, the interaction of the laser, microwave, or ultrasonic radiation with the particles is only to produce cavitation, transient local heating, or acoustic streaming. These physical forces then function to disrupt membranes and interstitium (e.g., rupture tumor blood vessel walls and cancer cell membranes) to enhance delivery of macromolecular drugs into cancer cells. See col. 2, lines 30-38, col. 4, lines 37-52, Fig. 1b, and Figs. 2-9 of Esenaliev. In contrast, according to the present invention, the nanoparticles absorb the energy from one or more of the recited forms of radiation and locally emit secondary ionizing electrons (in addition to fluorescent photons), which result in damage to surrounding tissue. In contrast, it is within the common knowledge of those skilled in the art that the forms of radiation recited in the present claims, such as x-rays, do not cause heating or agitation. That is, distinct from the forms of radiation taught by Esenaliev, the forms of radiation recited in the present claims do not cause heating or agitation of nanoparticles. Therefore, those skilled in the art, in following the teaching of Esenaliev, would have had no reason to look to the forms of radiation recited in the present claims, let alone to combine with the teaching of Finkelstein.

Furthermore, Applicants respectfully submit that the Examiner's characterization of the secondary reference to Finkelstein is inaccurate. Finkelstein merely discloses gold sodium

thioglucose (GTG), which is distinct from gold nanoparticles having a surface layer of thioglucose of the present invention. GTG is an ionic gold compound, whereas gold nanoparticles having a thioglucose shell have gold in the zero oxidation state. The biological ramifications of metals in different oxidation states are profound (e.g., sodium, which is in the zero oxidation state, vs. sodium ions in sodium chloride). Some of the differences include solubility, molecular weight, osmolarity, size, structure, density, and melting point. In other words, metal ions and metals in the zero oxidation state are two completely different chemical entities, and as a result, have extremely different properties *in vivo* including different blood retention times, pharmacokinetics, bio-distribution profiles in tissues, biochemical effects, clearance rates, toxicities, and pharmaceutical effects. Moreover, GTG is taught in Finkelstein to treat arthritis, which is entirely unrelated to the presently claimed methods of enhancing the effects of radiation by the administered nanoparticles. Finkelstein provides no motivation, in fact no reason, for those skilled in the art to apply a thioglucose shell to nanoparticles, which are used to absorb radiation (e.g., x-rays) and treat tumors.

In view of the foregoing, it is respectfully submitted that the rejection of claims 15-16 under 35 U.S.C. §103(a) based on Esenaliev in combination with Finkelstein is overcome. Withdrawal of the rejection is respectfully requested.

Claim 18 is rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Esenaliev in view of Lang, Jr. et al. (U.S. Patent No. 4,515,954).

The Examiner admits that Esenaliev fails to disclose metal polyanions complexed with quaternary salts for use in radation enhancement. However, the Examiner contends that Lang, Jr. et al. (hereinafter Lang) teaches a metal chelate useful for inhibiting the growth of

tumors, particularly a metal chelate complexed with non-toxic quaternary ammonium salts for effectively treating cancers such as leukemia.

In the first instance, Applicants reassert that Esenaliev does not teach or remotely suggest anywhere using any of the recited form of radiation in connection with nanoparticles in a radiation therapy. As discussed above, Esenaliev fails to provide sufficient teaching as a primary reference to support an obviousness rejection on this basis.

Furthermore, Applicants respectfully submit that the teaching of Lang is irrelevant because the compounds described therein are not metal polyanions. The compounds described by Lang are bases (col. 2, line 62), typified by having one or more nitrogens that can be protonated to form a positively charged species. An example of an organic base is triethylamine. Bases are either neutral (free bases), or if protonated, become cations. If compounds contain nitrogen with four substituents, such compounds are termed quaternary ammonium cations, which would be polycations. However, Lang does not disclose any polyanions or metal polyanions. Furthermore, all of the compounds described by Lang contain only a single metal atom (col. 1 and 2) and cannot be considered metal nanoparticles.

In view of the foregoing, it is respectfully submitted that the rejection of claim 18 under 35 U.S.C. §103(a) as allegedly obvious in view of Esenaliev in combination with Lang is overcome. Withdrawal of the rejection is respectfully requested.

Claim 23 is rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Esenaliev in view of Patel (U.S. Pub. No. 2005/0180917).

The Examiner admits that Esenaliev fails to disclose a particular concentration of metal to be achieved within the tissue treated. However, the Examiner contends that Patel teaches the treatment of cancer at the site of, and area adjacent to, the tumor via irradiation of the

diseased tissue. The Examiner alleges that Patel teaches nanoparticles comprising a metal, such as gold, at a concentration of about 0.1% by weight in Paragraph [0042].

As discussed above, Esenaliev fails to provide sufficient teaching as a primary reference to support an obviousness rejection. Moreover, Applicants respectfully submit that the Examiner's understanding of Patel's disclosure is incorrect. Patel is focused entirely on neutron capture therapy and therefore any material used for this must contain elements that have reasonable neutron capture cross sections, namely the isotopes listed by Patel: ^{10}B, ^{6}Li, ^{22}Na, ^{22}Co, ^{123}Co, ^{126}I, ^{135}Xe, ^{148m}Pm, ^{149}Sm, ^{153}Eu, ^{155}Gd, ^{157}Gd, ...(See Paragraph [0036]). It is these isotopes that provide the potential therapeutic effect upon bombardment with thermal neutrons. These isotopes may be in the form of micro or nanoparticles. Patel also discloses that the nanoparticles containing the active isotope(s) listed above may also contain small amounts of additional metals, such as V, Mn,...gold (Au) .....(See Paragraph [0042]). These elements have very low neutron capture cross sections and are not useful for neutron capture therapy. The purpose or benefit of including these bystander elements with the neutron capture isotopes is not discussed in Patel. However, it is the concentration of these metals in the nanoparticles that Patel is referring to, i.e., these additional metals can be present <u>in the nanoparticle</u> "at a concentration of about 0.0001% wt/wt to about 0.1% wt/wt" .....(See Paragraph [0042]). This percentage clearly refers to the concentration of the metal elements in the nanoparticles (composed mainly of active neutron absorbers), <u>not</u> the percentage of nanoparticles in the target tissue as recited in the present claims.

In view of the foregoing, it is respectfully submitted that the rejection of claim 23 under 35 U.S.C. §103(a) as allegedly obvious in view of Esenaliev in combination with Patel is overcome. Withdrawal of the rejection is respectfully requested.

Claim 25 is rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Esenaliev in view of Cash, Jr. et al. (U.S. Patent No. 6,125,295).

The Examiner concedes that Esenaliev fails to disclose x-ray radiation emitted in the range of "1 keV to 25,000 keV." However, the Examiner states that Cash, Jr. et al. (hereinafter Cash) teaches the presence of heavy elements to enhance dosage to target tissue in radiotherapy. Cash allegedly discloses the use of an x-ray apparatus with an output in the range of 30 keV to 150 keV for treating a tumor.

Applicants reassert that Esenaliev does not teach or remotely suggest anywhere using any of the recited form of radiation in connection with nanoparticles in a radiation therapy. As discussed above, Esenaliev fails to provide sufficient teaching as a primary reference to support an obviousness rejection on this basis.

Furthermore, the teaching of Cash is directed to the use of a contrast agent, especially iodine, in combination with focused x-rays, in radiosurgery. Cash does not teach anywhere the use of nanoparticles for the enhancement of radiation. Esenaliev, as discussed above, employs particles in combination with means for mechanical disruption of membranes and interstitial regions to enhance delivery of a required drug. The approaches of these two patents are very different. Therefore, there would have been no reason for those skilled in the art to combine the respective teachings.

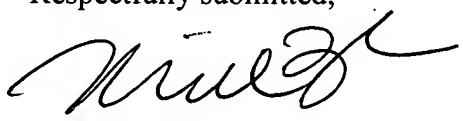
Accordingly, it is respectfully submitted that the rejection of claim 25 under 35 U.S.C. §103(a) as allegedly obvious in view of Esenaliev in combination with Cash is overcome. Withdrawal of the rejection is respectfully requested.

With respect to new claims 44-68, Applicants respectfully submit that these claims define the claimed methods as *consisting of* administering nanoparticles and irradiating the tissue

or the population of cells. In this regard, Applicants observe that Esenaliev teaches irradiating particles by pulsed laser light (in the range of 0.2 μm to 2 μm) or microwaves to heat the particles, or by ultrasound to agitate the particles. According to Esenaliev, such treatment of particles would rupture tumor blood vessel walls and cancer cell membranes, thereby enhancing microconvection in the interstitium to improve delivery of macromolecular drugs into cancer cells. See col. 2 lines 30-38, col. 4, lines 37-52, Fig. 1b, and Figs. 2-9 of Esenaliev. This is distinct from the present invention where nanoparticles are used to enhance the radiation effects, not to enhance drug delivery. Esenaliev does not teach enhancing the effects of radiation of any form by using nanoparticles, as presently claimed. Nor does Esenaliev teach ablating unwanted tissue or cells, e.g., a tumor, by irradiating nanoparticles administered to such tissue or cells, *in the absence of any drug*. Accordingly, Esenaliev does not teach, or suggest by any means, the invention as claimed in claims 44-68.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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